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VOL. V. NO. 2.

STORAGE

DECEMBER, 1911

TRANSACTIONS

OF THE

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.

London:
SOCIETY OF TROPICAL MEDICINE AND HYGIENE,
11, CHANDOS STREET, CAVENDISH SQUARE, W.

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Proceedings of a Meeting of the Society on Friday, November 17th, 1911.

Sir WILLIAM LEISHMAN, F.R.S., *President*, in the Chair.

FURTHER CONTRIBUTIONS TO THE ETIOLOGY OF BERI-BERI.*

BY DR. H. SCHAUMANN.

In compliance with the invitation with which this Society has honoured me, I will try to give you a short report of my latest investigations concerning the etiology of beri-beri and a summary of the deductions.

At the end of this lecture I should like to epitomise the conclusions which I have drawn from the latest observations and my own work.

As these experiments are, however, closely connected with many of my previous researches, I think a short recapitulation will give you a better view and make the main results of my work clearer.

My first investigations were made on food suspected of causing ship beri-beri and extended to the possible poisons, including oxalic acid and pathogenic fungi, contained in the suspected articles of food. The possible lack of amylolytic and proteolytic enzymes, of proteine and of mineral salts, have also been the subjects of these researches. As all these experiments gave negative results and the calculation of the contents of proteine, carbo-hydrates and mineral salts in the rations employed in the diet also showed that there was no question of a lack of

* At the conclusion of his paper Dr. SCHAUMANN showed an interesting series of lantern slides, illustrating the experiments on animals referred to in his paper.

these nutrients, I thought that a lack of phosphorus in the diet might perhaps be connected with the origin of the illness. This view was confirmed by the fact that many particularly suspicious articles of food which caused beri-beri in man and polyneuritis in animals contain very little phosphorus.

Many articles of food, however, become pathogenic only by long storage or artificial processes (long cooking or extraction). Therefore if the lack of phosphorus in the diet had any connection with the illness, it could not be a question of very stable compounds, such as inorganic phosphates. The assumption that a deficiency of phosphorus in the diet might be the essential etiological factor in polyneuritis, particularly beri-beri, was supported by the slight urinary excretion of phosphorus observed by me in the cases of beri-beri and ship beri-beri patients in the Seemanns-Krankenhaus* in Hamburg. This lack of phosphorus, which had already been noticed by SCHEUBE and other students, was confirmed by these researches. What also strengthened this idea was, that organs rich in phosphorus compounds, as, for instance, the nerves and spinal cord, were chiefly attacked by beri-beri. Rabbits which had been fed on Indian corn exclusively and had died with paralysis showed osteoporosis, and this affection could also be attributed to a deficiency in the metabolism of phosphorus. Self-preservation, the tendency of all that is alive to maintain its equilibrium, or to re-establish it, whenever disturbed, in the quickest and safest way, induces the organism evidently to spare where this economy can be practised with a minimum of danger for its existence, and so the bones in the present case seem to be sacrificed in order to protect other organs, rich in phosphorus too, but more important for life. As previous investigations, executed in order to ascertain whether the presence of poisons, or the lack of proteine or proteolytic and amylolytic enzymes or mineral salts in the articles of food, might be the cause of experimental polyneuritis in animals or beri-beri in men, had given a negative result, and as nothing seemed to be in favour of these suppositions, I thought they could be abandoned. Further examinations of the stores of sailing ships, on which cases of ship beri-beri had occurred, showed that the content of phosphatides in peas and of definite organic phosphorus compounds in beans had suffered a considerable

* Sailors' Hospital.

reduction, and that the salt meat had lost a great proportion of its original phosphorus content. The presence of purin bases in the brine further proved that the nucleoproteids of the salt meat had also undergone a decomposition.

My experiments with animals showed the following results :—

Polished rice, as already known, given to pigeons caused polyneuritis in about four weeks, and the birds died after 30 to 40 days, with pronounced lameness, and after having lost about 41 per cent. of their original weight.

If the rice had been repeatedly extracted with water and dried, the pigeons fed exclusively on it died on an average after 12 days, and a loss of weight of about 26 per cent. only.

The chemical test of the rice used showed it had lost only 3·43 per cent. of its original contents of proteine, but, on the other hand, nearly 36 per cent. of phosphoric acid (P_2O_5).

A monkey fed on extracted rice exclusively died after previous paralysis of the posterior extremities on the 73rd day of the experiment.

Rabbits fed only on Indian corn suffered from pareses of the hind-legs and died after severe paralysis, frequently accompanied by spastic convulsions. Minced horse-flesh which had been heated from one to three hours in autoclaves to 130° with a solution of carbonate of sodium, and then neutralised with hydrochloric acid, caused decided paralysis in dogs, cats and rats.

The cats and dogs, which at the beginning of this diet had still gained, and only subsequently lost weight, died emaciated after an average of 50 days, severely lamed. The rats, which were lamed but had hardly lost weight, were still alive after 80 days with only one exception.

On the other hand, rats fed exclusively on rye bread, previously heated to 120° with a carbonate of soda solution in an autoclave, and then neutralised with hydrochloric acid, died with pronounced signs of paralysis and greatly emaciated.

The same results were noticed in rats fed on a mixture almost free from phosphorus, consisting of potato-starch, sugar, albumen and mineral salts, to the exclusion of inorganic phosphates. The addition of inorganic phosphates to this food was also ineffective.

The animals, lamed as described, were, as a rule, quickly cured, and occasionally in a surprisingly short time by a series of substances con-

taining a great proportion of organically combined phosphorus. Amongst these, proved to be especially effective, are rice-bran, yeast, wheat-bran, phaseolus radiatus (Katjang-idjoe), testiculin prepared from bull testes, and codfish spawn.

A particularly notable trial was made with a goat, fed alternately on Indian corn and polished rice. It lost weight, and after a time its hind-legs became paralysed, then it received a slight addition of phaseolus radiatus, and I succeeded, with this intermittent treatment, in gradually producing an illness remarkable for its chronic character, and in this sense analogous to human beri-beri.

The goat's extremities were completely paralysed after five months. Then it was fed on green food, given large doses of phaseolus radiatus and yeast, after which the paralyses lessened very slowly. Finally, the goat was fed for a fortnight upon polished rice and Indian corn only and was then killed.

The microscopic examination executed by Dr. H. DA ROCHA LIMA showed very distinct degenerative signs in the spinal cord and in the peripheral nerves.

Further tests with animals showed that a comparatively small addition of rice-bran, yeast, testiculin, wheat-bran and phaseolus radiatus to the food-stuffs, which given alone produced polyneuritis, were able not only to keep the animals in good health but to maintain the balance of nutrition. In fact, the original weight frequently increased from the very commencement of the experiment, and proved the far-reaching favourable influence of these additions, although their quantity was relatively small.

Yeast-lecithin and, to a slight degree also, nucleinic acid proved their suitability for prolonging the test-animals' lives.

Phytin, protylin and ovolezitin had no obvious effect, whilst inorganic phosphates, glycerophosphate of calcium and metaphosphate of albumen artificially prepared from metaphosphoric acid and albumen were known to have even a bad effect. The results of a few organic compounds are striking when given to pigeons previously lamed through feeding them exclusively on polished rice. Nucleinic acid, for instance, effected an extraordinary but only temporary cure of completely paralysed pigeons. The birds were able to run about and fly after one or two small doses, but in spite of several repetitions of the dose they became lame again in a few days and died.

Occasionally the examinations of the nerves of the paralysed animals showed no anomalies, but in most cases there were more or less clear signs of degeneration, and these were sometimes very advanced. It was further ascertained that the nerve degeneration caused by pathogenic food-stuffs was slighter the longer pigeons previously lamed by it had additions of protective stuffs to this food. It seems, therefore, that a gradual regeneration of the nerves was effected by this process.

In the case of a dog fed on denaturised horse-flesh, and which had received a daily ration of 3·4 g. of chloride of calcium, scorbutic symptoms were associated with the paralyses. Extensive ulcerations and erosions formed on the gums, palate and tongue. The spleen, liver and kidneys were very swollen, and hæmorrhages occurred in the latter. It is possible, therefore, that a disturbance of equilibrium in the metabolism of calcium besides phosphorus plays a part in scurvy.

This supposition gains in probability from the observations made by TANAKO MASAHIKO undertaken for quite a different purpose. MASAHIKO observed that dogs and rabbits to which large doses of soluble or insoluble salts of calcium had been administered, alone or simultaneously with phosphate of sodium, always showed severe hæmorrhagic diathesis, especially manifesting itself in ecchymosis of the mucous membrane of the stomach. Considering that the appearance of scurvy is frequently attributed to eating much salt meat, and that the sea-salt used in the brine often contains considerable quantities of calcium and magnesium salts, this is not an improbable association.

Whether, however, this is so, and whether the metabolism of chlorine and other factors do not come also into question with the etiology of scurvy, can naturally only be decided after further and more thorough investigations. Professor AXEL HOLST'S latest publications, as well as those of FRÖLICH and FÜRST, demand the greatest attention in this respect.

I should like to mention here a few observations concerning ship beri-beri.

The examinations of the food-stuffs suspected of causing the disease gave, as already mentioned, the following results—there was no proof of the presence of any kind of toxins in the examined foods.

The schizo and hyphomycetes gained from dried beans and peas, and further cultivated on moist bread, and given to a dog for some length of

time, did not act pathogenically. The further chemical examinations showed, however, that the dried and long-stored leguminous foods had lost considerably in phosphatides.

I think, however, that the destruction of another frail constituent of fresh food is also probably of great importance due to the pathogenic effect produced by long storage or heating of an originally harmless diet. I will speak of this stuff and its peculiar qualities later on, and only mention now that the repugnance caused often by a long-stored provender to the crews of sailing vessels is probably due to the lack of this factor.

The leguminous foods, such as dried peas and beans often retained their hardness even after cooking, so that they were hardly eatable. This circumstance seemed to me to be in a causative connection with the decrease of phosphatides, as, according to OVERTON'S experiments, the lecithines, which belong to the phosphatides, play an important part in the osmosis of the cellular membrane in general, and, in the present case, of the cellular membrane of the dried peas and beans. Very extensive changes were shown in salt meat. Much albumen was extracted from it by the brine, and especially a great deal of phosphoric acid, which latter occasionally decreased as low as one-tenth of the contents in fresh meat. The presence of purin-bases and trimethylamin in the brine proved that the phosphoric acid extracted by it was, in part, due to organic compounds of phosphorus. A number of articles of food which were taken from the stores of beri-beri ships caused polyneuritis in animals fed solely upon them, as AXEL HOLST has already observed. However, a dog, which was fed on salt meat and preserved potatoes in conjunction, became ill too, and died after severe lameness.

As I have mentioned in the introduction, my earlier and already published experiments gave no assurance that poisons or a deficiency of proteolytic and amylolytic enzymes, or of proteine, or of mineral salts could come into question as causative factors of beri-beri. And also the calculations by which the proportion of the main nutrients—proteine, carbo-hydrates and fat—in the suspicious food were ascertained showed that the single daily rations of this diet contained sufficient quantities of the main nutrients for the daily need of a man. Also the diet used by FLETCHER and FRASER, in their well-known experiments with cured and uncured rice, contained sufficient quantities of these nutrients

to exclude the suspicion that a deficiency of one or more of these could be regarded as the cause of the illness. On the other hand, the quantities of substances, preventives of polyneuritis, added to the diet in my experiments, contained such small quantities of these nutrients just mentioned, that the favourable effect of these additions could not be attributed to them, that is, to the well-known nutrients, which were considered up to date as sufficient for the maintenance of the equilibrium in the organism. Judging by the results of the experiments made by me with the addition of a mineral salt mixture most similar to the ashes of food to a pathogenic diet, the favourable effect of the protecting additions could just as little be attributed to the mineral salts ingested with them. The stuffs which act protectively and differ in general greatly in their other ingredients have, however, as a common and characteristic quality, a large proportion of organic phosphorus compounds. So there remains only the possibility of attributing their efficacy chiefly to this, but not exclusively, as I will argue later on. Besides the already mentioned facts, the following are liable to prove the accuracy of this view :—

1. The effect of the protective additions was directly proportionate to their content of P_2O_5 in the case of yeast, rice-bran and wheat-bran with varying P_2O_5 content.

2. The calculations of the constituent parts of the diet rations, used by FLETCHER and FRASER in their experiments, showed that the essential difference lay in the content of organically combined phosphorus. This was considerably greater in the dietary with cured rice, from which the persons experimented on did not contract beri-beri, than in the dietary with uncured or polished rice which resulted in cases of beri-beri. The quantities of all other nutrients, however, differed but slightly in both cases.

3. The chemical changes demonstrable in food which caused no ship beri-beri while fresh, but did so after long storage or other damage, were due chiefly to the phosphorus content in general, and especially organic phosphorus compounds.

4. All determinations of the urine and fæces, made by me in cases of beri-beri and ship beri-beri, pointed to a decided decrease of phosphorus in the organism. These statements are corroborated in the literature on the subject.

5. A parallel experiment executed with two rabbits, one of them being fed only on Indian corn, the other one only on dried peas, showed that the loss of phosphorus in the rabbits fed on Indian corn, which produces polyneuritis, was relatively great, whilst the retention of phosphorus in the rabbit fed on peas, which never caused polyneuritis, was remarkably pronounced, as was proved by the difference of the food taken and the excretions in both cases.

My further examinations were mostly concerned in ascertaining the organic phosphorus compounds, or some other factors upon which the favourable effect of the protective additions might depend.

Before continuing, I will say that in these investigations I have devoted special attention to rice-bran, in view of the surprisingly favourable experiments made with cured rice in Eastern Asia.

I proceeded in the following manner with my investigations concerning rice-bran. Dried rice-bran was extracted consecutively according to the usual rules with aceton, ether and alcohol of 96 per cent., and finally with 0·3 per cent. hydrochloric acid. The residuum of the rice-bran was then dried. The different solutions, with the exception of the hydrochloric solution, were evaporated at a low temperature, and the residuum of the alcoholic solution again extracted with absolute alcohol. This alcoholic solution was once more evaporated after filtering. The hydrochloric solution was mixed with double its own volume of alcohol of 96 per cent., through which mainly phytin was precipitated. The filtered solution was then carefully neutralised with carbonate of sodium, and completely evaporated to dryness in the vacuum. This residuum, which formed a yellow hygroscopic powder after being ground, I will, for the sake of simplicity, in future, call "hydrochloric extract." Of these extracts, the alcoholic and hydrochloric demand special interest, because they both appear to possess remarkable protective power. Of the alcoholic extract about 0·25 g., or about 6 grains per diem and head, proved themselves to be sufficient to preserve pigeons, which were fed only upon polished rice, from lameness for 80 days. However, the pigeons emaciated greatly under this treatment, and lost almost a third of their weight. A doubly increased dose of the alcoholic extract made no great difference in this, for in spite of it only a very small increase in the weight of the same pigeon emaciated by the previous treatment resulted. The effect of the hydrochloric extract was the same, only

larger doses had to be given, about 0·86 g. per day and pigeon being necessary to preserve the pigeons fed upon polished rice from manifest polyneuritis.

I notice that similar trials have been made by STANTON and FRASER with the same results. But my experiments showed further that one could restore even seriously paralysed pigeons with both preparations in a surprisingly short time. Dogs, also seriously lamed through being fed on denaturised meat, recovered in a surprisingly short time. The dogs, hardly able to move before the administration of the hydrochloric extract, could often run in about five hours' time after a dose of 10 g., and were quite lively in twenty-four hours.

A noticeable result of both preparations was their decidedly stimulating effect on the appetite, which compelled the animals to take much larger quantities of the pathogenic diet than they would have done without them. As the extracts were always given to the test-animals in the shape of pills and never came into touch with the food itself, there could be no question of an improvement in the taste.

It seems to me that here it is a question of the formation of a hormone, such as, for instance, the secretin, which, as you well know, is secreted by the pancreas, and enters the general circulation.

Secretin, as we know, exercises a decidedly stimulating effect on the appetite.

I will just mention here that I have noticed the same effect produced by rice-bran extracts, also by using other preparations, extracted from yeast and phaseolus radiatus. While these also protect the test-animals from manifest polyneuritis, the addition of small doses of phytin and yeast-lecithin only increased the appetite, without, however, guarding them against death.

The table which I have drawn up shows the difference in the stimulating effect of the different stuffs on the appetite.

PIGEON'S FOOD.—POLISHED RICE.

	Addition per day and pigeon.	Amount of food taken per day and pigeon.
1.	Without addition	6·99 g.
2.	0·5 g. Phytin	7·26 g.
3.	0·5 g. Yeast-lecithin	7·37 g.

PIGEON'S FOOD.—POLISHED RICE—*continued.*

	Addition per day per pigeon.	Amount of food taken per day and pigeon.
4.	1·00 g. Phaseolus radiatus-extract (prepared with pepsin and hydrochloric acid)	9·15 g.
5.	0·25 g. Rice-bran-phosphatide	9·85 g.
6.	1·00 g. Hydrochloric rice-bran-extract ...	11·29 g.
7.	0·50 g. Hydrochloric yeast-extract (purified with alcohol)	11·63 g.

I will just remark here that the pigeons fed on polished rice with a daily addition of 0·5 g. of nucleinic acid, phytin and yeast-lecithin, emaciated to an exceptional degree (about 52 per cent.) before dying and showed no decided pareses before, although the post-mortem frequently proved extensive degeneration of the nerves. Further experiments must show whether this extraordinary circumstance is general. I must add that the residuum of the rice-bran, extracted previous and successively with aceton, ether, alcohol, and 0·3 per cent. of hydrochloric acid, and still containing 0·81 per cent. P_2O_5, considerably delayed the death of the pigeons, which had eaten this residuum besides the polished rice; but this residuum could not protect the pigeons from polyneuritis.

On dogs, which were fed on denaturised meat, and whose appetite was very slight for some time before they were paralysed, the stimulating effect of the hydrochloric extract was very noticeable. After a dose of 10 g. they devoured the food which they had refused before, and so, as a rule, they gained in weight considerably at first. Both rice-bran preparations have also a lasting effect, particularly the hydrochloric extract. The after effect of a dose of 1 g. given to a pigeon which had been seriously lame, lasted ten days. A seriously lamed dog, which was dosed with 10 g. of hydrochloric extract, remained in good health nearly four weeks, after which paralysis set in again. With regard to the chemical properties of both these rice-bran preparations, which act protectively, it is noteworthy that the alcoholic extract is a phosphatide loosely combined to a carbo-hydrate. This phosphatide contains, as an analysis showed, all the characteristic components of this sort of compounds, that is, phosphoric acid, glycerine, choline and fatty acids. The preparation used in my experiments contained 0·558 per cent. P_2O_5. Hence its phosphoric content was small.

I succeeded in isolating from the hydrochloric extract, which is in the main a mixture of carbo-hydrates, a crystallised substance containing nitrogen but no phosphorus. I will test its chemical and physiological properties as soon as a sufficient quantity has been prepared. The hydrochloric extract used by me contained 1·648 per cent. P_2O_5.

I will remark here that FRASER and STANTON, CHAMBERLAIN and VEDDER, COOPER and FUNK, and also EIJKMANN, have recently reported about experiments which they have made with rice-bran preparations. These extracts, obtained by a different method, contained only a very small proportion of phosphorus or none at all, and proved to be efficient to a certain degree, even in small doses. These scientists therefore concluded that phosphoric metabolism could play no part in the etiology of beri-beri. I will return to this afterwards, but should like to remark that the effect of the different preparations used by me and those employed by the above-mentioned scientists is most likely due to one and the same fundamental substance with a highly remarkable mode of action, which I will now discuss.

It is plain it cannot be a question of the ingestion of nutrients with these rice-bran preparations, which have such an energetic and enduring effect if one considers the very small quantities which are efficient. The ingested quantity of nutrients is much too small to come into consideration for the supply of material for the formation of substance in the organism and also contain no, or far too little, phosphorus to cover the whole demand. The energetic, specific and long-lasting effect, already discussed, also refutes this view.

The physiological importance of this substance must therefore be some other, and can only be an indirect one. It must be attributed to the capacity of causing or favouring the absorption or assimilation, or both, of certain nutrients. One can suppose the mode of action to be a catalytic one, and assume the stuff in question to act as a catalysator, producing the synthesis of certain components of nutrients, originated by their digestion and subsequent decomposition.*†

One can also assume that it acts like an hydrolytic enzyme and causes the decomposition of certain nutrients to the degree necessary for their

* *Man kann die Wirkungsweise des bete Körpers als die eines Katalysators auffassen welcher die Synthese gewisser Spaltungsproducte aus Nahrstoffen bei der Verdauung entstehen vermittelt.*

† Splitting *(aufspalten)*.

absorption. This latter assumption, however, strikes me, for various reasons, as not being very plausible. The hypothesis that the activator acts like a catalysator seems more likely. HARDEN and YOUNG, IVANOFF and V. LEBEDOW have proved lately that the juice of yeast is able to produce the combination of hexoses (fructose, galactose and maltose) with soluble phosphates, the products of these syntheses being the phosphoric acid-esters of the hexoses mentioned, or the respective salts of these esters. I think that the processes in question here are much more complicated, still the instance quoted shows the possibility of similar reactions. At any rate, the protective substance, which I will call the "activator," can only play a mediating part in connection with the metabolism, and therefore I do not consider it of importance whether the activator in itself is free from phosphorus or not. The correctness of this conception is shown not only by theoretical considerations, specially by its slight consumption and its enduring effect, but also by the results of the experiments made. Two circumstances seem to me to strongly prove these results :—

1. The animals lose weight considerably, with the addition of the activator alone to pathogenic foods. On the other hand, with the addition of an equivalent quantity of the original substances, rice-bran or yeast, they do not lose weight, and remain quite healthy. In the first case, consequently, there is a considerable interference with the metabolism, but not in the second.

2. Nerve degeneration could always be proved, even if only in a slight degree, in all the pigeons experimented on by me for some length of time, with the phosphatide or hydrochloric extract of rice-bran. These pigeons had been fed, during the experiments, only on polished rice and finally killed.

If one considers in this the stimulating effect of the rice-bran preparations upon the appetite, and that consequently with a plus of food (polished rice), also a plus of nutrients, particularly of organically combined phosphoric acid contained in the rice is absorbed; if one considers further that by the effect of the activator the whole amount of organic phosphorus in the food may be better utilised, it is comprehensible that the activator is able to preserve the pigeons for a long time from severe degeneration of the nerves, and in the case of diseased birds cause a noticeable improvement. The activator alone, however, evidently is

not sufficient to completely protect the birds from nerve degeneration and preserve the equilibrium in the nutrition.

I must mention that I have been trying for some time to isolate the activator in a pure state, and expect to succeed.

EIJKMANN has reported briefly that the preparation used by him is also effective in hypodermic injections. By further experiments with the activator, or activators if there should be several, combined with different organic phosphorus compounds contained in food, I hope a better understanding of the mutual relations of these agents may be obtained. If one asks further, to which stuffs necessary for the maintenance of a complete equilibrium of nutrition the activator's effect extends, I think that the organic phosphorus compounds contained in the additions can only, or at least in the first place, be taken into consideration. Inevitable consequences of the deficient metabolism of phosphorus are, as many experiments cited in my monograph prove, a deficiency in the metabolism of nitrogen, and in accordance with the law of the minimum in the metabolism or nutrition in general. The reasons for this conception I have already mentioned, and I cannot repeat them here, for lack of time. I will only emphasise once more that the protective stuffs, rice-bran, yeast, etc., in the small quantities sufficient to keep animals in a perfect equilibrium of nutrition, contain so small quantities of the essential and well-known nutrients that they cannot come into question. The favourable effect of these protective stuffs can therefore, only be attributed to their common quality, which is the great content of organically combined phosphorus.

For lack of time also I cannot here enter into the subject of the importance of these observations for physiology in general, and especially the physiology of nutrition. I will only remark that this seems to be a very great one. In the present case the protective effect of the protective stuffs mentioned (yeast, rice-bran, etc.) is, as far as one can see, a combined one; that is, the effect is due, firstly, to the presence of organic phosphorus compounds; and, secondly, to the presence of the activator, which acts on these phosphorus compounds so that they can be properly and completely utilised for the metabolism.

If I should express my conception metaphorically, I would say the activator acts like a match setting fire to the combustibles, which are the organic phosphorus compounds, in first place. These, however, com-

municate the fire secondarily to nitrogen compounds, carbo-hydrates, and so on.

I will not discuss the question whether there is only one activator extending its effect to all different organic phosphorus compounds, or if there are several, every one being able only to act on determined organic compounds of phosphorus (lecithins, nucleoproteids, etc.). Further investigations must elucidate this question, and it may be that the problem is more complex still than it seems to be now.

The activator, or the activators, may be slightly combined with organic phosphorus compounds. This conception seems likely on account of the association of the activator and the rice-bran phosphatide.

Finally, I should like to draw your attention to the following points :—

Later examinations have shown the much greater similarity than one formerly assumed between experimental polyneuritis of animals and kakke, or beri-beri.

This similarity does not refer only to the etiology, as far as it is connected with the nutrition, but also to the pathological and anatomical alterations due to these diseases.

Therefore there seem to exist many more reasons for assuming that both diseases are at least intimately related to each other than to presume the contrary, chiefly by taking into consideration that the same cause must not necessarily have the same results in different organisms.

The extraordinary success obtained by FLETCHER, FRASER, ELLIS, and particularly by HEISER in the Philippines, solely by a change in the diet, can reasonably only be attributed to the change in the nutrition. There can be no question that the essential factor lies here in the giving of the rice-bran adhering to the cured rice.

As many reports show, the same result can however be attained by the addition of other food to polished rice, and therefore it is not an exclusive property of cured rice. For instances, peas, phaseolus radiatus and fresh meat may be mentioned. The activator itself and the organic phosphorus compounds rendered fit for use by it, are most likely contained in many articles of food, even though in very varying quantities.

The assumption that beri-beri is a disease caused by a deficient metabolism is favoured by the circumstance that there is not a single infectious disease which can be prevented exclusively by a change in diet, and which can be cured by such a change.

Far be it from me to completely exclude biological processes in the

etiology of beri-beri, although it seems to me that alimentary influences greatly predominate. It is possible that an abnormal flora and other parasites of the intestines may destroy the activator as well as the phosphorus compounds in question. Intestinal parasites and microbes might likewise injure the mucous membrane of the intestines, by which absorption could be hindered.

The effect must then naturally be the same as with an insufficient supply of the mentioned effective substances, and could therefore easily cause the illusion of an infection.

All the effects taken together seem to me, however, only to allow of one conclusion, that beri-beri is a disease due to a deficient metabolism of phosphorus and its consequences.

These tables epitomise the latest observations and my own work:—

RABBIT No. I.—FOOD: INDIAN CORN.

FOOD TAKEN.

Period 1911, from noon to noon.	Food consumed (Indian corn).	N.	P_2O_5	SO_3	CaO.	MgO.	Date.	Weight.
July 20 to 24 ...	56·4 g.	0·888 g.	0·433 g.	0·253 g.	0·053 g.	0·066 g.	July 20	3·120 g.
,, 24 ,, 31	269·2 ,,	4·240 ,,	2·065 ,,	1·208 ,,	0·256 ,,	0·313 ,,	Aug. 3	2·900 ,,
,, 31 ,, Aug. 7	311·3 ,,	4·902 ,,	2·388 ,,	1·398 ,,	0·296 ,,	0·359 ,,	,, 10	2·780 ,,
Aug. 7 ,, ,, 14	277·0 ,,	4·364 ,,	2·124 ,,	1·244 ,,	0·263 ,,	0·322 ,,	,, 14	2·700 ,,
July 20 to Aug. 4	913·9 g.	14·394 g.	7·010 g.	4·103 g.	0·868 g.	1·060 g.		−0·420 g.

EXCRETIONS.

Period 1911, from noon to noon.	With the	N.	P_2O_5	SO	CaO.	MgO.	Loss of Weight.
July 20 to 24 ...	Urine ...	3·243 g.	0·851 g.	0·324 g.	0·030 g.	0·196 g.	−190 g.
,, 24 ,, 31 ...	,, ...	3·329 ,,	0·942 ,,	0·370 ,,	0·287 ,,	0·221 ,,	− 30 ,,
,, 31 ,, Aug. 7	,, ...	1·966 ,,	1·199 ,,	0·561 ,,	0·178 ,,	0·403 ,,	120 ,,
Aug. 7 ,, ,, 14	,, ...	5·052 ,,	1·402 ,,	0·578 ,,	0·368 ,,	0·357 ,,	− 80 ,,
July 20 to Aug. 24	Urine ...	16·590 g.	4·394 g.	1·836 g.	0·863 g.	1·177 g.	−420 g.
,, 20 ,, ,, 24	Fæces ...	3·230 ,,	2·836 ,,	1·216 ,,	0·242 ,,	0·062 ,,	
July 20 to Aug. 24	Urine & Fæces ...	19·820 g.	7·230 g.	3·052 g.	1·105 g.	1·239 g.	

BALANCE.

Period: July 20 to Aug. 24, 1911.	N.	P_2O_5	SO_3	CaO.	MgO.
Food taken	14·394 g.	7·010 g.	4·103 g.	0·868 g.	1·060 g.
Excretions	19·820 ,,	7·230 ,,	3·052 ,,	1·105 ,,	1·239 ,,
Difference	−5·426 g.	−0·220 g.	+1 051 g.	−0·237 g.	−0·179 g.

RABBIT No. II.—Food: Dried Peas.

FOOD TAKEN.

Period 1911, from noon to noon.	Food consumed (Dried peas).	N.	P_2O_5	SO_3	CaO.	MgO.	Date.	Weight.
July 20 to 27 ...	6·1 g.	0·204 g.	0·060 g.	0·028 g.	0·001 g.	0·009 g.	July 20	2·730 g.
,, 27 to Aug. 3	300·0 ,,	10·053 ,,	2·940 ,,	1·401 ,,	0·054 ,,	0·444 ,,	,, 27	2·490 ,,
Aug. 3 to ,, 10	384·0 ,,	12·868 ,,	3·763 ,,	1·793 ,,	0·069 ,,	0·568 ,,	Aug. 3	2·600 ,,
,, 10 to ,, 14	165·0 ,,	5·529 ,,	1·617 ,,	0·771 ,,	0·030 ,,	0·244 ,,	,, 14	2·660 ,,
July 20 to Aug. 14	855·1 g.	28·654 g.	8·380 g.	3·993 g.	0·154 g.	1·265 g.		−70 g.

EXCRETIONS.

Period 1911, from noon to noon.	With the	N.	P_2O_5	SO_3	CaO.	MgO.	Weight. Loss or Increase.
July 20 to 24 ...	Urine ...	1·560 g.	0·447 g.	0·116 g.	0·006 g.	0·031 g.	−240 g.
,, 24 to 31 ...	,, ...	6·147 ,,	0·991 ,,	0·595 ,,	0·227 ,,	0·011 ,,	+110 ,,
,, 31 to Aug. 7	,, ...	9·117 ,,	1·344 ,,	0·619 ,,	0·206 ,,	0·256 ,,	+ 40 ,,
Aug. 7 to ,, 14	,, ...	8·716 ,,	1·619 ,,	0·819 ,,	0·118 ,,	0·287 ,,	+ 20 ,,
July 20 to Aug. 24	Urine ..	25·540 g.	4·401 g.	2·149 g.	0·557 g.	0·585 g.	− 70 g.
,, 20 to ,, 24	Fæces ..	0·184 ,,	0·137 ,,	0·064 ,,	0·025 ,,	0·018 ,,	
July 20 to Aug. 24	Fæces & Urine ...	25·724 g.	4·538 g.	2·213 g.	0·582 g.	0·603 g.	

BALANCE.

Period: July 20 to Aug. 24. 1911.	N	P_2O_5	SO_3	CaO.	MgO.
Food taken	28·654 g.	8·380 g.	3·993 g.	0·154 g.	1·265 g.
Excretions	25·724 „	4·538 „	2·213 „	0·582 „	0·603 „
Difference	+ 2·930 g.	+ 3·842 g.	+ 1·780 g.	− 0·428 g.	+ 0·662 g.

The loss of weight of the Indian corn rabbit in the beginning of the experiment is doubtless due to the circumstance that the test-animal refused the food, to which it was not accustomed, at first. As soon as it began to take the food a remarkable increase of weight immediately set in.

The loss of lime in the same rabbit is very likely only a consequence of the very small amount of CaO in this specimen of dried peas, because a loss of CaO was never observed in previous experiments with rabbits fed exclusively on dried peas.

THE ETIOLOGY OF BERI-BERI.

By Professor AXEL HOLST, of *Christiania*.

I beg to start with some remarks concerning the etiology of beri-beri as it occurs among Norwegian crews. The disease appears on long voyages and, in the great majority of cases, on tropical waters. We have, however, also seen cases on Arctic voyages and, during the last years, on the Antarctic ocean. The symptoms are, on the whole, those of the wet beri-beri of the tropics and Japan. As for neuritis, I have formerly been of the opinion that neuritis was seldom to be met with. I based this opinion on the communications of some other authors. During the last four years I have, however, seen personally a good many Norwegian sailors suffering from the disease, and the great majority, perhaps all of them, suffered from neuritis, though the symptoms were, to a large extent, rather slight ones.

The disease was rather rare on board Norwegian ships till 1894. After that year it has, however, been frequent. This frequency coincides with some alterations of the food on board Norwegian ships on long voyages, introduced by a new scale of diet of the same year. These alterations represent the first part of this paper. Having already mentioned most of them in a paper read before the Epidemiological Society of London in 1907, I shall limit myself now to some short remarks.

Norwegian crews eat but little rice. In fact, with a few exceptions, Norwegian sailors, suffering from beri-beri, have either not eaten any rice at all, or they have only once or twice a week eaten one or two spoonfuls of it in their soup. Consequently rice cannot be the cause of their disease. Norwegian crews, however, eat bread as the staple of their daily food. I beg to start with this bread question.

Till 1894 our sailors used, on long voyages, biscuits baked of rye-flour with bakers' yeast. If pigeons are fed on rye-bread, no matter if it is baked with or without yeast, they do not get any neuritis. After 1894, however, the sailors have been obliged to bake soft bread on board. For this purpose they either use wheat-flour or wheat and rye-flour in equal proportions. On long voyages, however, Norwegian sailors never use bakers' yeast, because they do not know how to keep it.

If pigeons are fed on wheat-bread, they always die with Eijkmann's neuritis, sooner, if the bread is baked without, later, if it is baked with yeast. As for the said mixture of wheat and rye-flour, I have only made experiments with bread baked without yeast. This bread, too, produces neuritis on pigeons.

As far as wheat-bread is concerned, these experiments have been repeated with a similar result by SIMPSON and EDIE, who experimented on chickens. Consequently, as far as we are able to judge from animals, the staple of the daily food on board Norwegian ships on long voyages is of the same dangerous quality as the polished rice of eastern countries.

It may, however, be objected that, for instance, millions of people in France daily eat wheat-bread as the staple of their food without getting any disease from it. The explanation of this fact is probably to be found in their eating other food as well. These neutralise the dangerous influence of the bread. It may, therefore, also be of interest to know some other alterations in the food of Norwegian sailors introduced by the said scale of diet of 1894.

Till 1894 the sailors ate almost daily, for dinner, salt meat and peas. After this year, however, the use of these nutriments has been reduced to once or twice a week. Since that time they have had tinned meat three or four times a week (at present mostly twice a week), tinned fish once a week, and dried fish once a week.

As for tinned meat, this has been boiled in the factories at temperatures exceeding 100°C., as a rule for one hour at about 120°C. Basing myself on some important researches of GRIJNS, of Java, I pointed out, in my paper of 1907, that such meat, when the only food produces Eijkmann's neuritis on chickens, and that this disease even appears when the meat only is boiled for half-an-hour at 110°C. If, however, fresh meat is boiled for a corresponding time at 100°C., GRIJNS and afterwards myself have found that the disease does not appear.

Though this probably is of importance, I doubt whether it is quite so important as I have believed formerly. Because in some experiments -but not in others- I have found, during the last year, that salt meat, too, even when boiled for one hour at 100°C., produces the disease. I may add, that the salt meat, which gave the positive result, was somewhat tainted.

At present I attach greater importance to the considerable reduction of the peas mentioned. As stated in my paper of 1907, peas prevent Eijkman's neuritis. In fact, these protective properties are exactly the same as those of the famous Katjang-idjoe beans that GRIJNS has found to prevent the neuritis of poultry, and that KIEWIET DE JONGE and HULSHOF POL have proved to cure and prevent human beri-beri. Very probably, therefore, peas also prevent beri-beri of man. Under these circumstances, the Norwegian Government has sent considerable quantities of ordinary peas, of the same sort as used on board ships, to Java, where Dr. DE HAAN, Dr. GRIJNS and, above all, HULSOF POL, have promised to carry out experiments with them on man. These experiments could, however, not start until this autumn, and have not yet been finished.

The second part of my paper concerns the possibility of a connection between beri-beri and scurvy. This connection has often been discussed—for instance by GRIJNS, SCHAUMANN, SIMPSON and EDIE and others, but above all by NOCHT in Hamburg. About ten years ago he pointed out that ship beri-beri almost only appears on long voyages on board sailing-ships—that is under circumstances where sailors do not get fresh provisions for a long time. And, *vice versa*, as soon as crews suffering from beri-beri get fresh provisions, above all fresh vegetables, surprisingly often they recover rapidly. These experiences agree with those daily seen in Norway; but they also agree with the facts so well known from the history of scurvy.

But there are also other facts that speak in favour of the said connection. It is true, in Norway, we do not often see beri-beri cases connected with pronounced symptoms of scurvy. But sometimes we see them, and on the other hand, there exist in the literature several observations concerning cases of scurvy showing symptoms of a neuritis. Some years ago I personally met a Russian, who had been put in prison in Russia, where he had suffered from severe and typical scurvy. I asked him if he had also any anæsthesia of the legs and feet. Yes, he had. I therefore asked him to write to three of his fellow-prisoners staying at that time in Paris, who also suffered from scurvy. He got a reply from two of them; they, too, had anæsthesia of the legs and feet.

But there are some experimental facts also, speaking in favour of the

same connection. For instance, in another paper, read before the Epidemiological Society, 1907, Dr. FRÖLICH and myself pointed out that guinea-pigs, when fed on different sorts of grains, groats or bread, die from a typical scurvy, showing loose teeth, typical hæmorrhages and the peculiar changes of the bone-system specific to human scurvy. If, however, fresh vegetables—for instance, fresh carrots, fresh salads, or fresh cabbage, are added to the grains, these additions prevent the disease. The same vegetables also prevent human scurvy; and they prevent and cure, as just mentioned, at least to a large extent, human ship beri-beri, too. But they also protect, as proved by Dr. FRÖLICH and myself, against the experimental neuritis of pigeons.

I beg also to draw attention to the following facts:—If you feed a pigeon on polished rice, it dies with neuritis. If you feed a guinea-pig on the same nutriment, and it lives long enough, it dies with a typical scurvy with or without some, but not much neuritis. But if you feed a pig on polished rice, it dies with both diseases—a pronounced scurvy and a pronounced neuritis. It may be added, in the first place, that there exist, in the literature, communications on cases of human scurvy after polished rice during the siege of Paris and, some years ago, in Hamburg (FRÄNKEL). In the second place, pigs get a combination of scurvy and neuritis, even when fed exactly on the same nutriments as used by Norwegian sailors on long voyages (bread, salt and tinned meat, dried potatoes), even when the bread is baked of pure rye-flour with yeast.

But there exist, on the other hand, some facts speaking against a relationship of the two diseases. It is true, Dr. FRÖLICH and myself have found that the anti-scorbutic constituents, for instance, of fresh cabbage are, to some extent, soluble in acids, but not in petrol-ether, and that they dialyse. These reactions agree with some of the results found by FRASER and STANTON and SHIGA and KUSAMA, with regard to the anti-neuritic compounds of the polishings of rice. Dr. FRÖLICH'S and my own chemical researches are, however, not far advanced, and this is due to the fact that the anti-scorbutic constituents of fresh vegetables suffer from a far greater fragility than the corresponding anti-neuritic substances hitherto studied. This represents a great difference indeed. For instance, if you dry fresh cabbage and keep it in an open vessel in your laboratory, it loses, within some months, its antiscorbutic properties. It is easy to show that this is due to the humidity in the air. On

the other hand, however, even if rye-flour is exposed for two years to a moist air, it does not produce neuritis when given to pigeons. This seems to prove that the anti-neuritic constituent of the rye-flour is not destroyed by humidity. I may also add that the polishings of rice, and peas, being excellent protective remedies against the experimental neuritis of poultry, do not prevent the experimental scurvy of guinea-pigs. And still you may make peas prevent the latter disease; as Dr. FÜRST in Christiania has proved, the peas prevent the experimental scurvy when you moisten them and make them 'sprout. That is, they must be converted to a fresh vegetable. These preventive properties are not destroyed if the peas are boiled for one hour at 100°C. The same applies to grains such as oats and barley; if guinea-pigs are fed on these cereals before sprouting, they die from scurvy, if after sprouting, they do not get ill. Contrary to these results, however, GRIJNS has found that Katjang-idjoe beans, when sprouted and boiled for one hour at 100°C., lose their protective properties against the experimental neuritis.

Under these circumstances it ought to be of interest to examine the bone-system from post-mortems of beri-beri cases in order to ascertain if there possibly may exist some of the peculiar changes of the bone-marrow specific to scurvy. Dr. FRÖLICH and myself have also tried to carry out investigations of this kind; Dr. VIS, of Java, having been good enough to send us several ribs from about thirty post-mortems of beri-beri cases in Java. It is true, we did not find any changes of the said nature. These researches are, however, not conclusive, as all patients in question were more than twenty years; in fact, almost all of them were much older. The alteration of the bone-system, which is specific to scurvy, is however strictly limited to the process of ossification, that is, to the age below eighteen years.

Under these circumstances, Dr. FRÖLICH and myself think it safer to limit ourselves to a neutral expression, and imagine that there must exist, somewhere, a bridge between beri-beri and scurvy; but we cannot tell if there exists a real relationship. When, for instance, fresh cabbage prevents both the experimental neuritis and the experimental scurvy, the explanation possibly will be this: that the cabbage contains two different compounds, the former preventing one and the latter the other disease.

Finally, Mr. President, I thank you most sincerely for the opportunity you have given me of taking part in this discussion, which is of the greatest interest to my own sea-faring people.

Dr. Fraser: On account of the prominence given to experiments on animals, it is possible to lose sight of the fact that we, as medical men, are concerned with the etiology of a disease which affects man, and is known as beri-beri. This disease occurs epidemically and endemically in many oriental countries; in every case of it neuritis is a prominent symptom; scorbutic symptoms I have not observed.

Experiments on fowls have proved to be of inestimable value in working out the etiology of beri-beri; the reaction in fowls is quite as delicate as and comparable with a reaction *in vitro*, but there is no necessity whatsoever to argue for or against the identity of polyneuritis in fowls and beri-beri in man.

I do not propose to weary you with the details of our researches; these are submitted in our reports, also in a paper now appearing in the *Journal of Tropical Medicine*.

Some years ago I was interested in the subject of toxic amblyopia; the nerve degeneration in that disease is confined to those fibres in the optic nerve forming the pupillo-macular bundle. Later when an opportunity presented itself of investigating beri-beri, I formed the opinion that this disease, in which only certain nerve fibres are affected, might have a similar origin, and that as the disease was mainly confined to rice-eaters an investigation of the rices associated with beri-beri might lead to a solution of the problem.

On arrival in the Federated Malay States I became acquainted with the work of Dr. Braddon and the Dutch investigators; their work was at that time almost unknown in this country.

Dr. Braddon claimed to have proved that beri-beri only occurred among those who consumed "uncured" or stale rice, and did not occur among those who consumed "cured" rice. His hypotheses had met with the most vigorous opposition from many of his colleagues, but eventually Government was persuaded by him to test its accuracy. For obvious reasons the investigation could not be carried out in a place where the disease was prevalent, nor in a jail; eventually Dr. Braddon found conditions which answered our requirements and a research was planned and carried out by us.

That investigation confirmed the accuracy of Dr. Braddon's statement so far as it concerned the difference in results obtained from feeding on those rices, but it was necessary to carry the work further and

determine why "uncured" rice was harmful and "cured" rice harmless.

Throughout the course of the inquiry samples of the rice issued were collected daily, and for the first time in the history of beri-beri investigation we were in a position to examine rices connected with outbreaks of beri-beri, a point of the utmost importance in the then state of our knowledge.

From "uncured" rice a poisonous substance was obtained, but from "cured" rice the poisonous substance was obtained in greater amount. That substance, we now know from the researches of Dr. FUNK, was in all probability choline.

By a method of section-cutting and staining, as also by experiments on fowls, Dr. STANTON and I demonstrated that "uncured" rice was harmful, because in the process of milling or polishing it had been deprived of the subpericarpal layers, and that "cured" rice was harmless because the subpericarpal layers had not been removed. We further proved that "uncured" rice was equally harmful, whether freshly prepared or stale.

The terms introduced by Dr. BRADDON having thus been shown to be inappropriate we substituted the terms "polished" or "white" for that of "uncured," or "stale" and "unpolished parboiled" for that of "cured."

The results were compatible with those of TAKAKI, and also with those of EIJKMANN, provided that we substitute subpericarpal layers for the term silver layer or pericarp, which structure we have shown to be unimportant. Unpolished rice becomes harmful when cooked by steam under pressure.

Substitute unpolished rice or unpolished parboiled rice for polished rice in the diet of those who consume rice as the staple, cook in the ordinary way and beri-beri cannot occur. Dr. SCHAUMANN has shown that the diets employed by Dr. FLETCHER and by us were deficient in organic phosphates, but Dr. SCHAUMANN was not in a position to carry out the analyses of those diets and calculations based on the data recorded in text-books we have shown elsewhere to be inaccurate.

Professor HOLST has brought forward evidence which seems to show that beri-beri and scurvy are not identical in their etiology. The isolation and identification of the active substance contained in the subpericarpal layers is a work of the greatest importance, and the results will almost

certainly prove of wider significance than we can at present appreciate, but until that work has been accomplished let us not confuse the known with the unknown.

Dr. C. J. MARTIN: The Society is to be congratulated in that on one evening it has been addressed by three such prominent workers in the subject. What struck me most to-night in the points brought forward by Professor AXEL HOLST, who has been working at the etiology of ship beri-beri for many years, and is one of the first authorities in Europe on this subject, is the fact that the diet of Norwegian sailors prior to 1897 only just contained an adequate quantity of some essential constituent, and that when by legislative interference the diet was refined, and white bread substituted for some of the rye bread and peas, the danger zone was entered.

Beri-beri and scurvy are etiologically, as Professor AXEL HOLST has been largely instrumental in showing, closely analogous diseases, but the essential substance lacking, or inadequately present, is, I believe, not the same in the two cases.

Drs. SCHAUMANN and FRASER, who have been working simultaneously in different parts of the world, have succeeded by extensive and careful experiments in confirming the early work of EIJKMANN, and to some degree extending it. EIJKMANN's conclusions regarding polyneuritis of fowls are, by their labours, now thoroughly established. By his splendid demonstration of lantern slides Dr. SCHAUMANN has made us realise, in a way which would have been quite impossible without actually witnessing the experiments, the rapid cures which can be effected by treating birds suffering from polyneuritis in an extreme degree with yeast and other substances. This method of showing that a particular substance contains the active principal, which was used in the first case by EIJKMANN, is of the greatest importance to experimental workers. It has materially lightened their labours, for to extract a substance from a food-stuff, then to feed animals for months with food to which this has been added, and wait for results, is often dreary work.

I find myself, however, quite unable to follow Dr. SCHAUMANN in his conclusion that beri-beri is a disease due to deficient metabolism of phosphorus. It seems to me clear, from all the experimental work, that the fundamental cause of the disease is the deficiency of some substance

which is only originally present in minute amount in any diet. This substance is nearly absent in the rice-endosperm, but present in the rice-bran, and also contained in beans, yeast, meat, etc., in varying amount. Until recently it was not known whether the substance contained phosphorus or not.

The work of Messrs. COOPER and FUNK in my laboratory has, however, proved that the substance (which is clearly Dr. SCHAUMANN'S activator) which cures birds suffering from polyneuritis in the miraculous manner described by him, contains no phosphorus. This substance is an organic base, the salts of which are stable. Dr. FUNK will tell us some more interesting facts about it directly. I am not yet sure, however, that the absence of a sufficient quantity of this base is the sole etiological factor, and Dr. SCHAUMANN'S observations indicate that it is not, but I am convinced it is the essential one. It is not improbable that a diet of polished rice is defective in other subsidiary respects also.

Physiological derangement occurs from the absence of some essential requirement just as readily as from the presence of some harmful substance. The only difference is that in the former case the effect is not manifested until the body has exhausted its supply. Recent developments in our knowledge of nutrition have supplied several analogies for this view of the etiology of beri-beri.

Apart from the daily supply of potential energy in the form of fuel, some portion of the nitrogen must be supplied in the form of particular amino acids, for the synthesis of certain internal secretions and the protoplasm of particular cells. Although the total amount required for many of these purposes is small, it can only be obtained from substances having one definite molecular configuration. I believe that both beri-beri and scurvy are to be explained along these lines.

The study of beri-beri is at present attracting considerable attention, but it has now got into a comparatively easy stage. We must not forget, however, the much greater difficulties of observers in the early days, such as EIJKMANN, VORDERMAN and BRADDON, who narrowed down the problem so that it could be brought into the laboratory. I was delighted to hear Dr. FRASER speaking so warmly of the work of LEONARD BRADDON, who had been indefatigable in collecting a great mass of epidemiological and clinical evidence relating to the causation of beri-beri. To the analysis of this data he has brought to bear the greatest

scientific acumen, and the adoption of his recommendations had already, to a large extent, solved the problem of beri-beri in Government institutions in the Malay States.

Sir THOMAS BARLOW: I am not competent to discuss beri-beri from personal experience, but I am greatly interested in the disease, and especially so in the close relation which has been indicated this evening by Dr. HOLST between scurvy and beri-beri. There seems no doubt that study of the chemical changes involved brings these two diseases into close apposition. Much has been learned of the pathology of the former disorder by comparison of the changes found in young and adult subjects, mostly noticeable, as one would expect, in the developmental lesions of the bones, which are very manifest in children. Possibly these changes which are seen so readily in infants at the time of the eruption of the teeth, may have their counterpart in beri-beri, and something may be gained by the study of that disease in very young subjects, and in cases where the mother is suffering from beri-beri and is suckling her infant. There is another point with respect to polyneuritis which in beri-beri is attributed either to a toxin or a deficiency in blood supply affecting the nerve trunks, but which, from the researches described to-night, appears to be singularly amenable to diet changes. Now in infantile scurvy, extreme weakness of the limbs is a pronounced feature, and I have hitherto believed that this symptom was entirely due to subperiosteal hemorrhage, or to hemorrhage into the muscles, and consequent filtration of serum into the intermuscular planes. I still believe that what I have described is the chief factor in the powerlessness of the limbs in a severe case, but it would be exceedingly interesting if it should be found that there are also changes in the nerve trunks similar to those described in beri-beri. The remarkable improvement referred to with respect to the mobility of the limbs in beri-beri when the diet is altered is paralleled by what occurs in infantile scurvy. I trust that if opportunity occurs for the examination of beri-beri in young subjects the condition of the bones and muscles as well as the nerves may be further investigated.

Sir PATRICK MANSON: So far as beri-beri is concerned, I am afraid that I belong to a past age. I will confine myself to asking a few

questions that may indicate the necessity for caution in adopting the new views. (1) Are the experimental polyneuritis in animals and beri-beri in men the same disease? (2) Again, how can the epidemics of beri-beri which frequently occur in populations living on unpolished rice be explained? (3) How on this theory can fulminating cases be accounted for? (4) Another difficulty is suggested to my mind by the rapid cure of pigeons and other animals as reported by Dr. SCHAUMANN. PEKELHARING and WINCKLER and others have shown that in tropical beri-beri there was always marked and extensive nerve degeneration, Can that be cured in a few hours? Professor HOLST in the course of his remarks stated that animals fed on wheaten bread alone developed dropsical beri-beri, whereas animals fed on a mixture of wheaten and rye bread developed neuritic beri-beri. Some time ago I had two Norwegian seamen in hospital, lying in adjacent beds. One had well-marked dropsical beri-beri, the other equally well-marked atrophic beri-beri. As both men came from the same ship and sickened at the same time, are we to infer from Professor's HOLST's experiments that these sailors had fed on different rations?

Mr. CASIMUR FUNK: As the history of the subject of beri-beri has been already sufficiently discussed to-night, I propose to come directly to my experimental work.

In beginning this research I at first made some experiments with yeast and confirmed the statements of SCHAUMANN, that birds suffering from polyneuritis were cured by this substance. Afterwards I thought it would be interesting to hydrolyse the yeast in order to find out if after hydrolysis with 20 per cent. H_2SO_4 during 20 hours the comparatively simple hydrolytic products were still capable of curing. Experiment showed that this was the case. From this result it was obvious that the curative substance is a very stable body in acid solution and also established the probability that this is a basic substance of simple chemical nature.

These results were then applied to the investigation of rice-polishings.

The polishings were extracted with alcohol containing gaseous hydrochloric acid, and the extract after being freed from alcohol and fatty substances was precipitated with phosphotungstic acid in acid solution.

The precipitate formed was decomposed and proved to be strongly curative. This precipitate was found to be free from phosphorus, proteins and carbohydrates.

The filtrate from phosphotungstic acid was found inactive.

The solution of phosphotungstate decomposed contained a mixture of bases, mostly choline, and the curative substance was separated off from the liquid by means of $AgNo_3$ and $Ba(OH)_2$. The precipitate when decomposed by H_2S showed strongly curative properties in doses corresponding to 4 mgr. of nitrogen.

From the curative fraction it was possible to separate off a small quantity of crystalline nitrate of a base. As the material was extracted it was possible however to perform only one analysis and two cures. The crystalline substance corresponds roughly to the formula $C_{12}H_{18}0_4N(HNO_3)$ and will be further investigated.

In conclusion it might be stated, that the curative substance from rice-polishings is an organic base, having perhaps some connection with the lipoids, or, what is more probable, with the cerebrosides of the nervous tissues.

Dr. SIMPSON: There can be little doubt in the minds of those who have heard the interesting papers to-night that beri-beri is a disease of metabolism, due to the deficiency of some constituent in the food. The work of FRASER and STANTON, and others, has disproved the conception of it being an infectious disease; SHIGA, especially, has made numerous investigations to obtain evidence of bacterial or protozoon infections or toxins, and has failed to do so in spite of his unrivalled experience.

In discussing questions such as these we should not lose sight of the fact that the association between myxœdema and cachexia strumipriva in animals was formerly vigorously combated; the equal similarity in causation, pathology and cure between beri-beri and experimental polyneuritis in man justifies us in regarding them as identical. There are minor differences, but œdema is often found in animals with polyneuritis, and the photographs shown by Dr. SCHAUMANN answer Sir PATRICK MANSON'S question as to the occurrence of fulminating cases of polyneuritis in animals analagous to fulminating beri-beri in man.

I can contribute very little to the interesting discussion to-night, but the numerous experiments carried on in the laboratory at Liverpool lead us to agree with Dr. SCHAUMANN in regarding the problem as of considerable complexity. Only the simplest extracts appear to preserve the full protective power of natural foods; extracts prepared by complicated methods can prolong the life of the animals but do not restore them fully. For example, birds gained twice as much weight in three days' treatment with yeast as in three weeks' treatment with large doses of Chamberlain-Vedder extract. We may yet find a more complex mother substance with full protecting powers in the natural food-stuffs. Just as the discovery of the internal secretion of the thyroid has led to the recognition of other diseases due to other internal secretions, so the solution of this problem should throw light on other diseases. I may mention that Dr. MACAULEY has written me recently from South Africa, where scurvy was formerly rampant among the labourers, that as a consequence of a change of diet by Government orders, that disease is now less frequent, but there is still a large incidence of other diseases, such as pneumonia, cachexia, ulcers of the legs, etc. He has noted too that there are differences between mealie meal and mealies, which exactly parallel those demonstrated by Dr. FRASER in polished and unpolished rice. Undue "civilisation" of foods undoubtedly tends to the increase of disease.

Dr. SCHAUMANN: I should like to say with reference to the objections made by Dr. FRASER, that my conclusions were originally and chiefly formed from the observations made on the use of non-pathogenic food-stuffs containing, as a rule, a relatively large amount of organically combined phosphorus, and that I found that those which are prejudicial are mostly deficient in organic phosphorus compounds. But I have not based my deductions only upon this single fact. In my monograph I have extensively put forward a number of facts and observations which I have briefly mentioned to-day, and which corroborate my interpretation concerning the etiology of experimental polyneuritis and beri-beri. Among these observations there is a parallel experiment *(stoffwechselversuch)*, which helps to confirm my conclusions.

Dr. FRASER told us that it is impossible to say what was the phosphorus content in the food supplied in FLETCHER'S experiments.

I must object here that König's Handbuch gives complete analyses of all the food-stuffs employed by FLETCHER in these experiments, and so I was enabled to make approximate calculations of the amounts of the main nutrients and also of the phosphorus content in the daily rations by adopting the standard contents. I will remark besides that the phosphorus content in every single one of these food-stuffs does not differ very much in different samples, that is, the difference of the maximum or minimum content of phosphorus in one and the same article of food, even if it is of different origin, is not great. As I have adopted for my calculations the standard content of the main nutrients, I could prove that there was in every daily ration a sufficient amount of fats, carbohydrates and proteine. The only deficiency was in the amount of phosphorus, and this deficiency persisted also when the calculations were based upon the maximum content of phosphorus in polished rice.

What I said about the relation between experimental neuritis in animals and beri-beri in men, was not that both diseases are identical, as Dr. FRASER supposed. I will repeat what I have said about it, namely, "that there seem to exist many more reasons for assuming that both diseases are at least intimately related to each other than to presume the contrary, chiefly by taking into consideration that the same cause must not necessarily have the same results in different organisms."

With regard to the activator, only a minute quantity (according to the observations of Dr. FUNK, three milligrammes per day) is sufficient to preserve a pigeon from manifest neuritis for some length of time. I must object here, however, that experimental neuritis and, very likely, also beri-beri are diseases of nutrition, and therefore the addition of so small a quantity of any substance alone cannot be considered sufficient *per se* to prevent these diseases. The activator can only play a mediating part in the metabolism, and act upon one or more ingredients of the food, enabling the organism to utilise them.

Referring to what Sir PATRICK MANSON has said about fulminating cases of beri-beri, I venture to point out that I have observed in dogs cases very similar to those observed in pigeons, which Dr. SIMPSON has designated, in accordance with my own observations, as fulminant, and the symptoms of which Dr. SIMPSON has so very clearly described to-day. The degree of paralysis does not coincide always with the amount of

degeneration of nerves, which can be ascertained microscopically by the staining methods known up to date. The conclusions to be drawn from these observations seem to be, that the pareses and paralyses do not depend only on morphologic alterations, but also, and perhaps chiefly, on chemical or physical processes in the nerve tissue, due to the presence of certain stuffs, which are needed to furnish the peculiar energy for the function of the nerves.

Professor AXEL HOLST: In reply to a remark of Sir PATRICK MANSON, I beg to mention that not all pigeons fed on a mixture of rye and wheat flour die with œdema. As for the remarks of Sir THOMAS BARLOW, I forgot to call attention to some investigations mentioned in my printed paper. In fact, Dr. FRÖLICH and I have examined several ribs from each of about thirty beri-beri cases, that Dr. VIS, of Java, has been kind enough to send us. In these ribs we did not find the peculiar microscopical changes of the bone-marrow characteristic of scurvy. We found, however, another alteration of a somewhat suspicious nature. This alteration was very pronounced in all cases examined and consisted in a very marked rarefaction of the solid (compact as well as spongy) bone-substance of the foremost ends of the ribs. Though this rarefaction is not characteristic of scurvy, it is a prominent symptom of the disease.

As for the fact that we did not find the characteristic changes of the bone-marrow, I beg to repeat, what I have mentioned in my printed paper concerning the limitation of these changes to the process of ossification, that is to the age below 18 years. The patients whose ribs we have examined were, however, over 20 years; in fact, the great majority of them were much older.

BERI-BERI IN NORTHERN SIAM.*

BY

ARTHUR F. G. KERR, M.B.

In the years 1908 and 1909, Northern Siam was visited by a severe epidemic of Beri-Beri, which was confined to the valley of the Meh Ping, an alluvial plain almost wholly under rice cultivation. Chiengmai, the capital of Northern Siam, is situated near the centre of this valley.

This epidemic commenced in July, 1908, and reached its maximum in the November of that year. In 1909, the number of cases was considerably less than in 1908, and now (August, 1910) no new cases are reported. Previous to its appearance in July, 1908, the disease seems to have been almost unknown in this part of the country. A few native village doctors, on being questioned, said that they had seen a similar disease many years ago, but most of these men had no knowledge of any previous epidemic.

One case of beri-beri occurred in Chiengmai jail in August, 1904. This case, a male, told me that in the district he came from other people had the same disease, and several had died from it. The district from which this man came was one of those very lightly affected in the recent epidemic. No other case occurred among the prisoners till 1908, when there were two cases; in 1909 there was one case; and this year there have been, so far, no cases. The prisoners in this jail receive a small daily allowance, and buy their own rice, ready cooked, from market women at the jail gate.

Contrary to experience in other places, the scattered population of the country villages was much more severely affected than the town population, and all reports agree that the villages most affected were those in low-lying districts, where the ground is under water for the greater part of the rainy season.

I will shortly summarise some of the conditions of village life which may have some bearing on this outbreak.

Most of the villages are surrounded by rice-fields, and are, during the rains, almost as much flooded as the fields, the paths through them

* This paper was presented at the Meeting on November 17th, but not read.

being deep in mud. The buffaloes and pigs, both of which are usually kept beneath the houses, add no inconsiderable part to the general mire. The houses, for the most part, are built of bamboo basket-work, and thatched with grass or dry leaves; they are raised on posts four or five feet from the ground, and consist of a front open porch or verandah, roofed but open at the sides, and a back portion forming a single room, walled all round, with only one small door opening on to the porch; usually there are no windows. In this one room the whole family, often consisting of seven or eight persons, sleep, with the door shut. Even at mid-day this room is very dark, it is always dirty, and has a close, musty smell.

The rice is usually sown in July; when the young plants are two or three weeks old they are transplanted into the flooded fields. The harvesting of the rice begins about the middle of December and is completed early in January. Sometimes, if sufficient water can be obtained, a second crop of rice is sown about February and harvested in July.

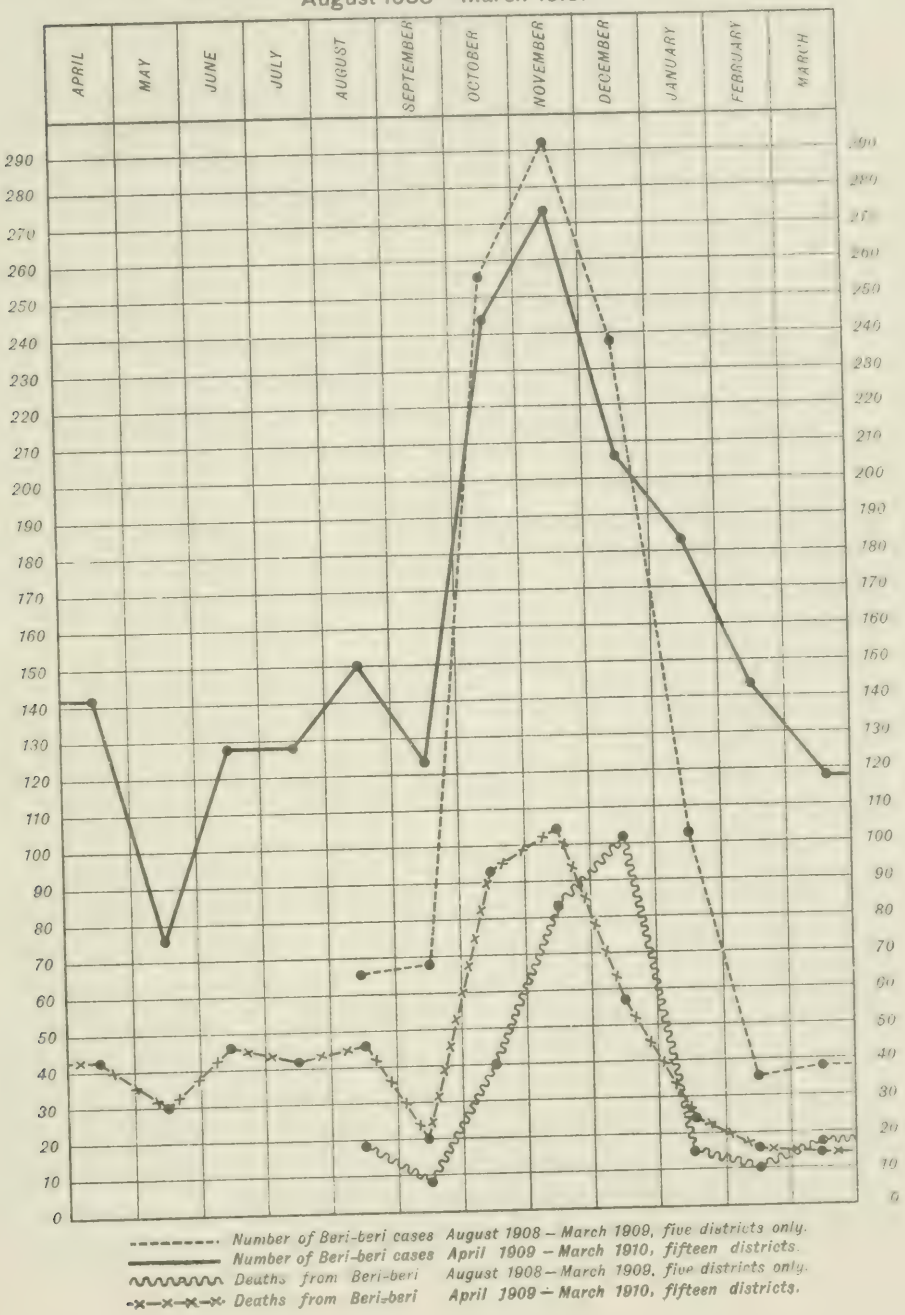
The rice is stored, unhusked, in round bins, made of bamboo basket-work, plastered with mud and roofed with grass; the bins are raised on posts three or four feet from the ground. For the most part only sufficient rice is husked each day for that day's consumption; occasionally enough is husked for two or three days' use, never more. The rice is husked by a pounder working in a hollow log, the pounder being attached to a lever worked by foot. Machine milled rice is unknown in Northern Siam.

It is difficult to point to any abnormal conditions as possible causes of this epidemic. There were late floods in 1908 and 1909, so that in many places the water was still standing in the fields when the rice was harvested in December; where this was the case the paddy had to be dried on platforms of bamboo built over the water, consequently much of it was imperfectly dried and became mouldy afterwards. However, when the epidemic started, about July, 1908, the rice of 1907—a good rice year—was being used, the 1908 rice not coming in till the end of December, when the epidemic was already declining.

As I have already mentioned, the rice of 1907 was good; nothing abnormal about it was noticed except that the young plants were eaten more than usual by caterpillars.

It will be seen from the chart that the number of cases rapidly rose in October and November, and from December fell as rapidly in both

Monthly prevalence of Beri-Beri in Northern Siam.
August 1908 — March 1910.



years. That is, the epidemic began to decline as the new rice was coming in, which might indicate that long-stored rice is more injurious than fresh rice. It must not be forgotten, however, that other conditions were changing at the same time—the land drying up, and the weather getting cooler.

If, as it has been suggested, beri-beri is a protozoal disease, the rise and decline of the epidemic may be intimately connected with the life history of the intermediate host of the parasite. The marked seasonal periodicity of this outbreak is, I think, evidence in favour of a parasitic origin.

There are some other points which tend to show a connection between the rice and this epidemic.

In Chiengmai itself, there were not many cases, but it was frequently noticed that one house had three or four cases, while the neighbouring houses were free. The members of one household all obtained their rice from one bin. In Chiengmai and other towns this rice comes from many different sources: it is usually bought in the open market—few of the town dwellers have fields of their own. In most of the town cases it was impossible to trace the source of the rice used; one house with three cases in a household of four, was known to have obtained rice from a district where beri-beri was rife.

In one of the out-villages, two out of three inmates of one house were down with beri-beri, and in a neighbouring temple with seven or eight priests, one was affected, and it was found that this priest was the only one in the temple who obtained his daily supply of rice from the above house.

On the whole, the evidence of this epidemic lends support to those theories which would connect beri-beri with rice, whether as containing a toxin, or directly or indirectly carrying a parasite. It seems opposed to the theory which regards beri-béri as a disease of metabolism, associated with a diet deficient in organically combined phosphorus, this deficiency being due to excessive shelling and polishing of the rice grains. Against this theory also is the fact, that many persons, as in the present epidemic, recover without making any change in their diet. Beri-beri has also been epidemic in other places, and died out without any change of diet being made, as Dr. WELLINGTON, in a paper read before this Society (Vol. II. p. 226) has pointed out. In some places,

however, there seems good reason for regarding over complete shelling of rice as at least a predisposing cause of this disease.

In explanation of the chart, it should be pointed out that returns of diseases were first made in 1908, chiefly on account of the beri-beri epidemic; and in that year only five out of fifteen districts sent in returns complete enough for inclusion on the chart: the first returns sent in that year were for August, a month after the beginning of the epidemic. These five districts have a population of about 120,900, the whole fifteen districts about 333,700.

Two of the ten districts not included for the first year were badly infected: one of them, with a population of 24,367, reported 233 cases and 48 deaths for October alone. The exclusion of these ten districts in the first year has lowered the number of cases at least one half, probably more, consequently the chart does not show the great decline of the disease in the second year, for which returns from all the districts are included.

NOTES AND COMMENTS.

BERI-BERI IN THE NAVY.

By Fleet-Surgeon P. W. BASSETT-SMITH.

The following facts relating to the Naval Service are, I think, of present interest, bearing on the question of the prevention and cure of beri-beri :—

For about ten years there has been a number of cases occurring in ships employed in the Persian Gulf; during the past few years, owing to gun-running operations, the conditions of service have been more severe, namely, the monotony of life, want of exercise, great heat, and difficulty of getting fresh provisions (fresh fruit and vegetables being almost unobtainable).

Fleet-Surgeon Mundy, R.N., reports that out of 182 natives in 1909, there were 19 cases and 7 deaths. Unmilled rice only was then served out; in 1910, with 317 natives, there were only 2 doubtful cases. In 1910, however, beri-beri appeared among the Europeans, who practically eat no rice. Out of 1,600 men there were 17 cases with 2 deaths and many invalided. Measures were taken to supply fresh fruit and poultry to the blockading ships' companies, which was done, and cases ceased to be recorded.

It would then appear that some of those conditions which we know predispose to scurvy were present here, and that the introduction of anti-scorbutic remedies was effective in stopping the epidemic among the Europeans.

NOTES ON THE INCIDENCE OF BERI-BERI IN THE SINGAPORE LUNATIC ASYLUM.

Illustrating Charts supplied by Dr. H. J. GIBBS, *Medical Superintendent Singapore Lunatic Asylum.*

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1. The daily average number of patients in this Asylum was in—

1906	...	290	1908	...	326
1907	...	292	1909	...	344

2. The full native diet consisted of—

Rice	1½ lbs.
Fresh meat	¼ lb.
Salt or fresh fish	¼ lb.
Assorted fresh vegetables	6 oz.
Salt	½ oz.
Onions	½ oz.
Garlic	⅛ oz.
Lard	½ oz.

The fresh vegetables were mostly sweet potatoes, pumpkins, cucumber, large turnip-like radishes, spinach, young growing shoots of rice, a variety of French bean, and green tops something like turnip tops.

3. The accompanying charts for the years 1906 to 1909 were intended to illustrate a short paper published in the *British Medical Journal* of 2nd October, 1909, p. 935, entitled "Uncured Rice as a Cause of Beri-beri," by Dr. W. Gilmore Ellis, the then Medical Superintendent.

4. Experiments with rice for many years in this Asylum pointed to the advantage of an exclusive use of parboiled, and after using rice of this description for the first eleven months of 1906 without the occurrence of a case of beri-beri, it was decided to make one last systematic trial by placing all the patients, for periods of four months alternately, on the polished and on the parboiled variety.

5. In the charts which are here published—

Dotted line shows total deaths from all diseases.
Straight line shows deaths from beri-beri.
Dot-and-dash line shows number of cases of beri-beri occurring monthly.

From this it will be seen that all patients were placed on a diet in which the rice was polished from the 1st December, 1906, until the 1st April, 1907.

6. Beri-beri broke out early in February, 1907, the first case occurring on the 5th. In all there were 24 cases in February, 33 in March, and 6 in April, the last occurring on April 10th.

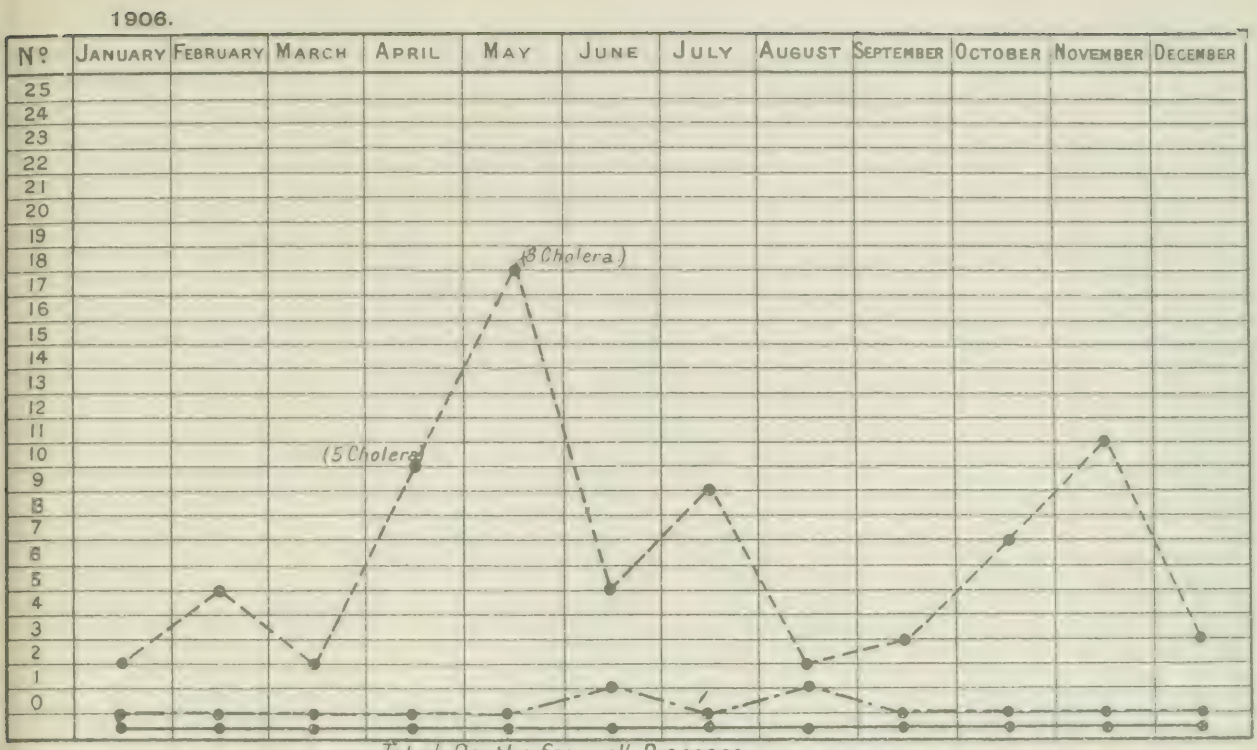
7. No further cases occurred, the inmates remaining on parboiled rice from April 1st until August 1st, when a return was made to the polished variety.

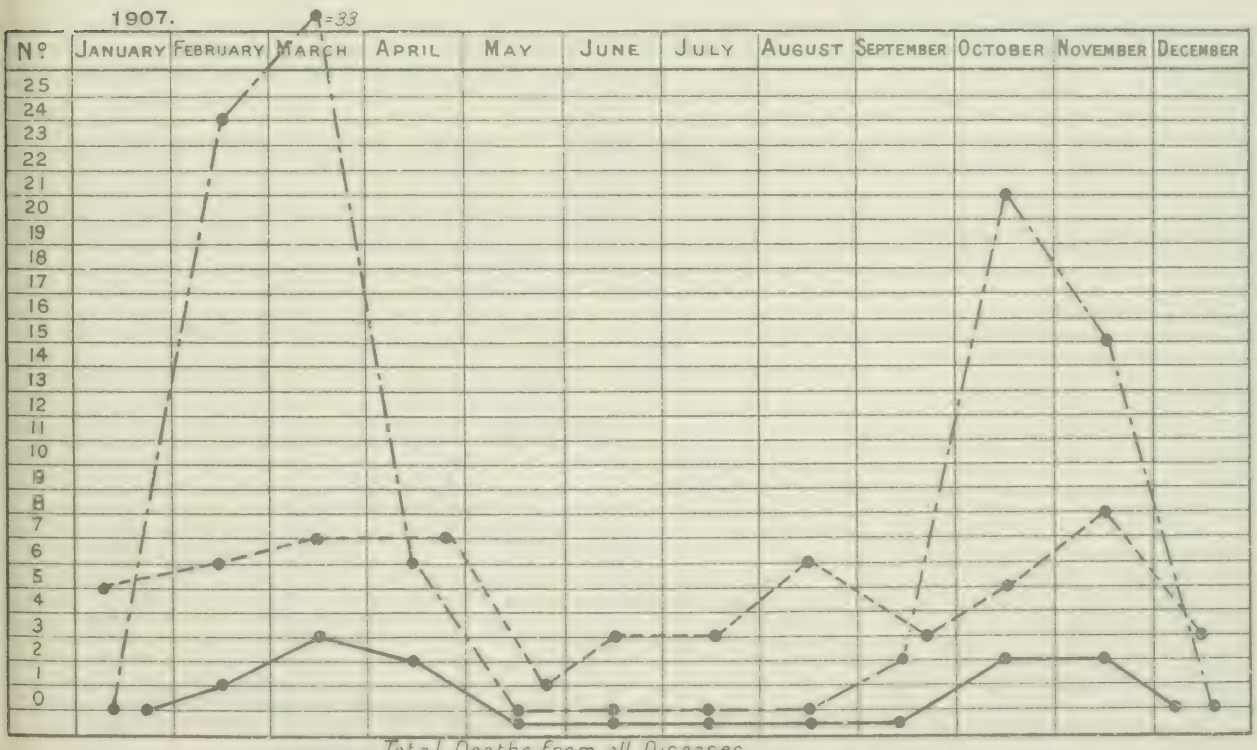
8. In September, 1907, beri-beri was once more in evidence, the first case being diagnosed on the 15th. The incidence was 2 cases in September, 21 cases in October, and 15 in November. Cases were breaking out so rapidly throughout the Asylum that a return was made to parboiled rice on 3rd November, instead of waiting until the end of the month, with the result that the outbreak ceased nearly immediately.

9. On April 1st, 1908, all inmates were once more given polished rice, the first case of beri-beri occurred on 26th May, other 17 cases had arisen by 10th June. And it was then determined to cease the experiment and to return finally to a diet of parboiled rice.

10. No other variety of rice but parboiled was used in the Asylum throughout the remainder of 1908, all 1909, and 1910 up to 20th December. No beri-beri occurred in the Asylum during this period, although the disease was prevalent as usual in the town of Singapore.

11. In December, 1910, at the suggestion of Dr. Highet, of Bangkok, and with his assistance, a supply of undermilled partially polished Siam rice was obtained. This variety is free from the objectionable colour of parboiled rice, is therefore considerably more palatable, and as will be seen from the charts for 1910 and 1911 no bad results have followed its use.

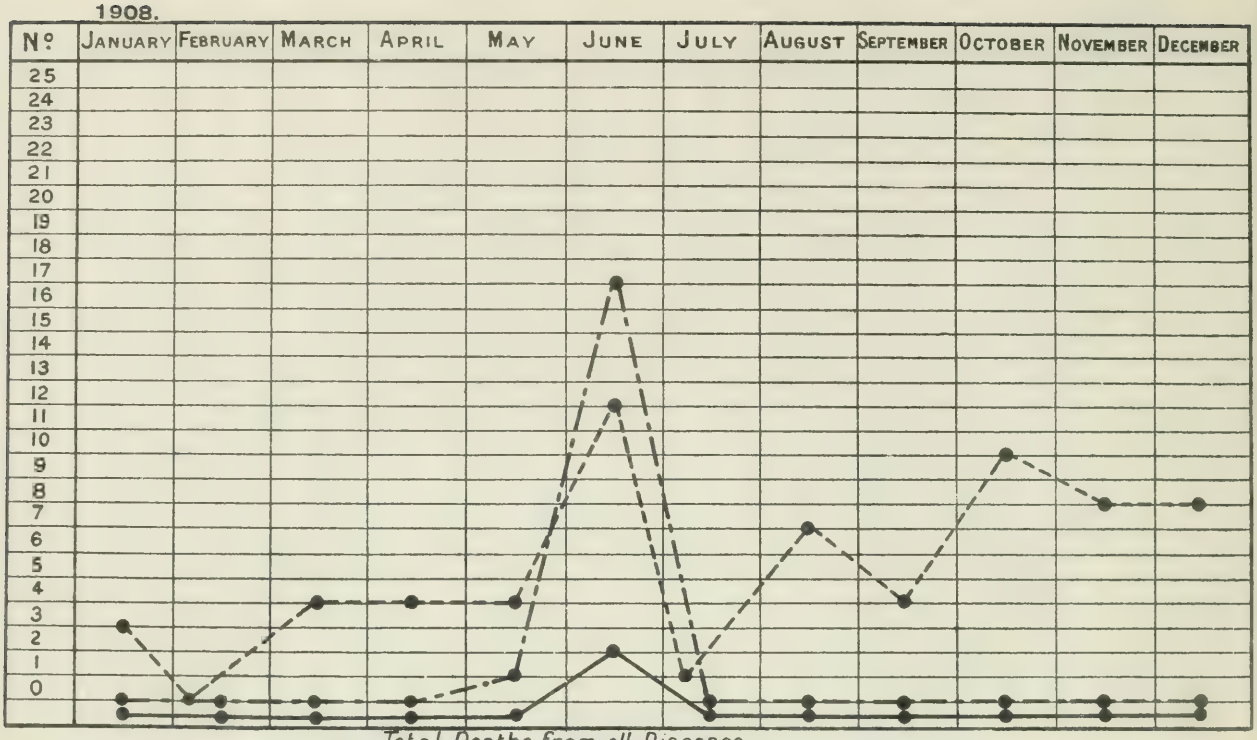




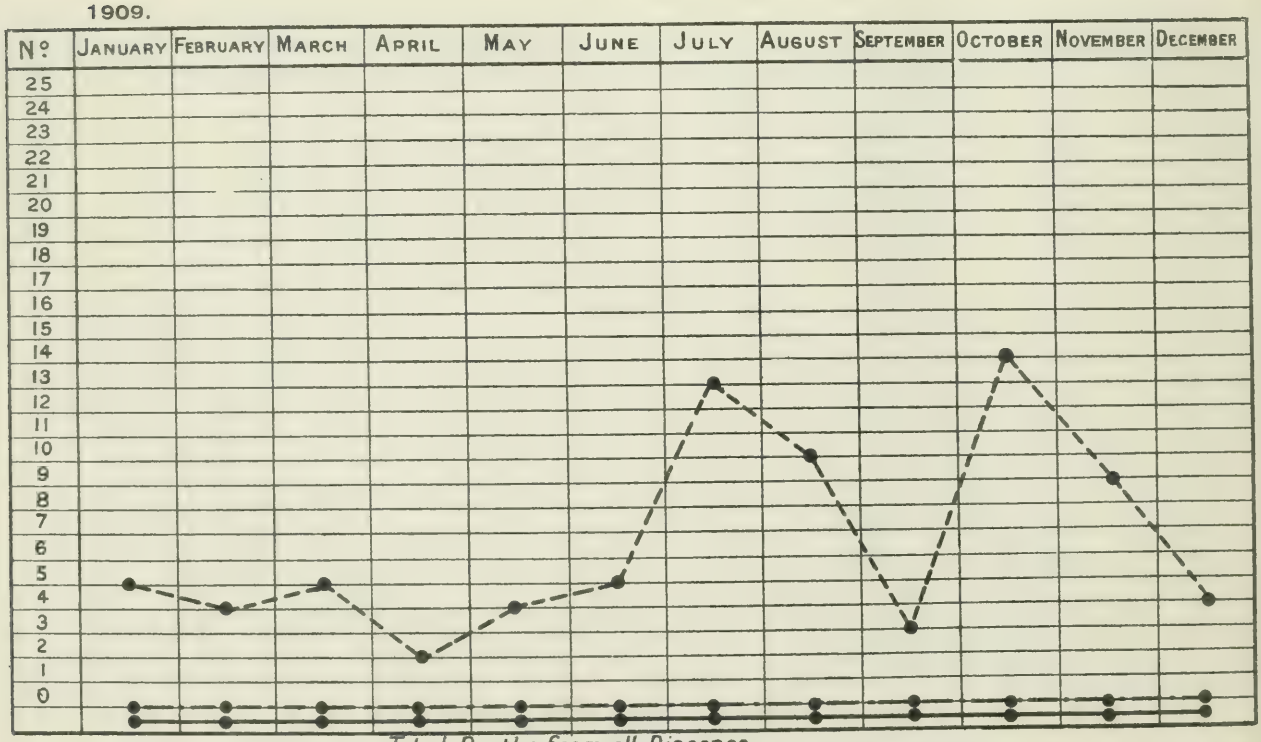
CHARTS illustrating the Incidence of Beri-beri in the Singapore Lunatic Asylum, supplied by Dr. H. J. GIBBS.

N.B.—Deaths from Cholera are shown in order to explain exceptional mortality.

1908.

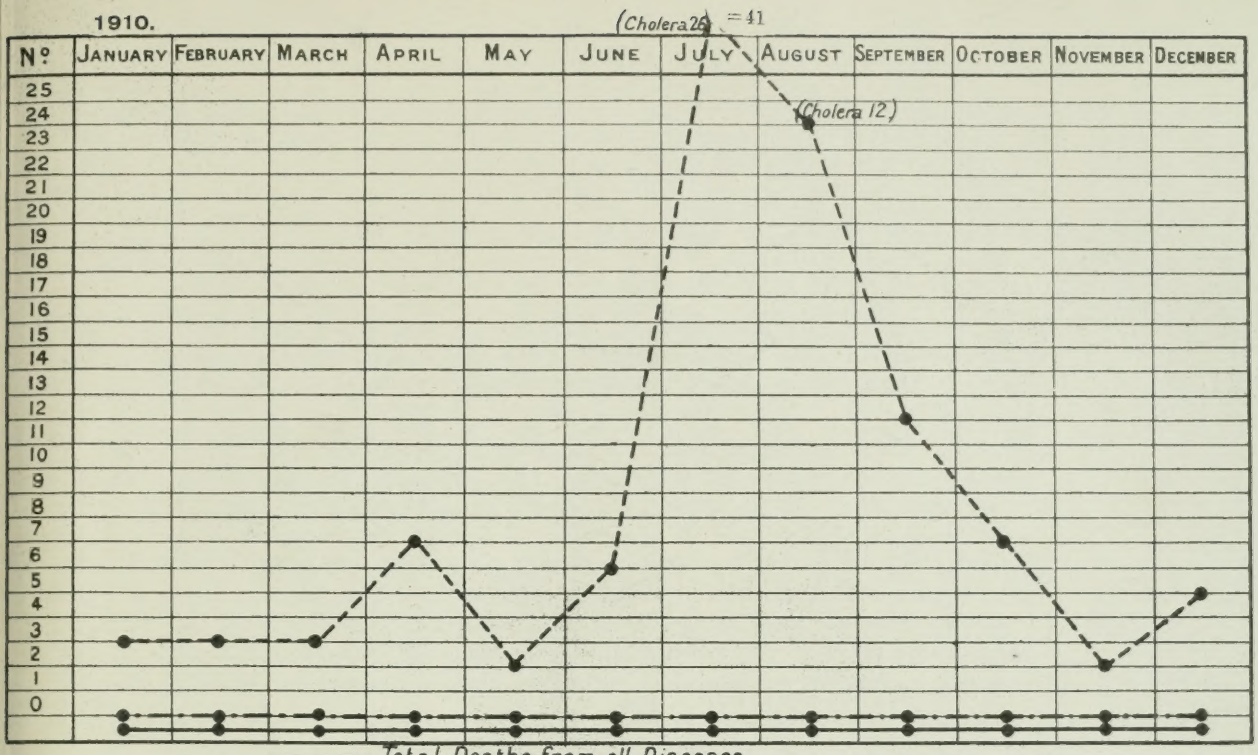


1909.



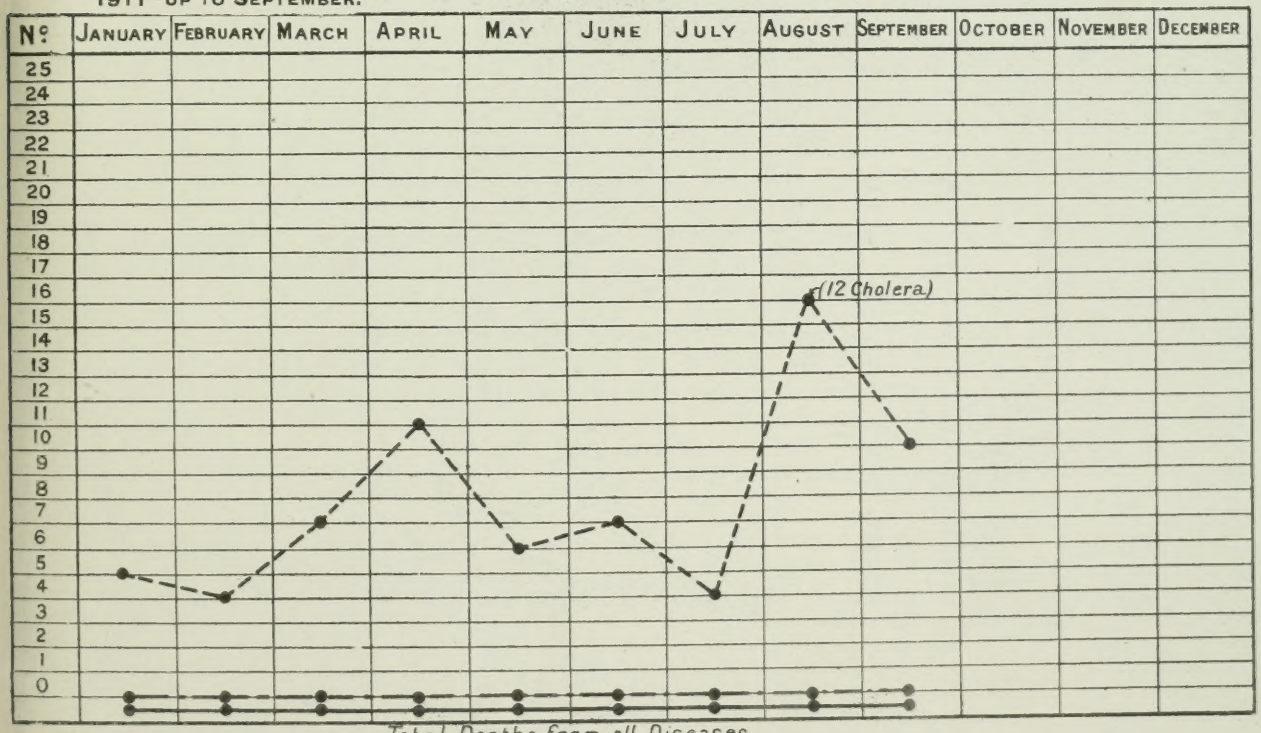
CHARTS illustrating the Incidence of Beri-beri in the Singapore Lunatic Asylum, supplied by Dr. H. J. GIBBS.

1910.



------ Total Deaths from all Diseases.
-·—·- Number of Cases of Beri-Beri occurring Monthly.
——— Deaths from Beri-Beri.

1911—up to September.



------ Total Deaths from all Diseases.
-·—·- Number of Cases of Beri-Beri occurring Monthly.
——— Deaths from Beri-Beri.

CHARTS illustrating the Incidence of Beri-beri in the Singapore Lunatic Asylum, supplied by Dr. H. J. Gibbs.

N.B.—Deaths from Cholera are shown in order to explain exceptional mortality.

QUESTIONS AND ANSWERS.

A.M.C.—Does the special form of Malaria exhibited in a first attack usually predispose to similar forms in future attacks? If so, should a patient whose first attack was of a comatose type be strongly recommended to live in a non-malarial country?

The type of fever manifested in one attack of Malarial Fever is very likely to be repeated in succeeding attacks if these are either relapses or due to a similar form of parasite, and if the other conditions of life and work are similar. It would therefore be the safest course to advise anyone who has suffered from a comatose type of fever not to return to a malarial climate. If however the patient was not in the habit of taking quinine prophylactically, and the severe symptoms could be traced to subsidiary and preventable causes, he might be permitted to return, provided he agreed to adopt a thorough method of malarial prophylaxis, including the regular taking of five grains of quinine a day.—C.F.H.

A.M.C.—Shallow trenching with subsequent utilisation of the ground for gardens seems to be the method best suited for applying to small native villages for disposing of dejecta. Would this method however tend towards propagating ankylostomiasis by the larvæ passing into the unturned soil and from there into the feet of the natives?

If the dejecta contain ankylostoma eggs, this would be an easy method of infecting (or re-infecting) labourers, unless they could be induced to protect their feet and legs by boots. Professor Looss and others have pointed out that these eggs in fæces can be destroyed by (1) burying them in the ground half a metre deep, provided there is no running water there, (2) exposing them for one day to dry sun heat, (3) mixing with an equal quantity of perchloride of mercury 1 in 200, (4) mixing with a quantity of water ten times the bulk, or (5) exposure to artificial heat at 45° C. or to freezing point. Of these (2) is probably the only one that would be feasible at Blantyre.

It is obvious that any means recommended must be easy of application, inexpensive and not hurtful to the soil or to the labourers. Common salt in a solution of two per cent. will kill young larvæ in laboratories and in mines, and Sir T. Oliver, in a paper read before the Tropical Society in January, 1910, recommended sulphate of iron in a solution of one per cent. He considers this "is well worth trying on a large scale."—F.M.S.

The Editor of the Transactions will be glad to receive questions concerning any department of Tropical Medicine and Hygiene, to be included in this column. These questions, if considered suitable, will as a rule be printed together with a short reply, but it will always be open to Fellows of the Society to send in their answers to these questions or to criticise opinions with which they may disagree. Thus it is hoped that this column may be of particular interest.

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